IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC., Plaintiff, v. MSN LABORATORIES PRIVATE LIMITED and MSN PHARMACEUTICALS, INC., Defendants.	C.A. No. 22-cv-228 (RGA) (JLH) (Consolidated)

DEFENDANTS' RESPONSIVE POST-TRIAL BRIEF ON NON-INFRINGEMENT

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Cases

TABLE OF ABBREVIATIONS

Term	Definition
'015 patent	U.S. Patent No. 11,098,015 (JTX-003)
'349 patent	U.S. Patent No. 11,298,349 (JTX-004)
'439 patent	U.S. Patent No. 11,091,439 (JTX-001)
'440 patent	U.S. Patent No. 11,091,440 (JTX-002)
'643 patent	U.S. Patent No. 6,030,643 (PTX-243)
Ansel	Howard C. Ansel et al., PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS, (7th ed., 1999) (DTX-363)
API	Active pharmaceutical ingredient
DTX	Defendants' Trial Exhibit
Exelixis	Plaintiff Exelixis, Inc.
Handbook	Raymond C. Rowe et al., HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (5th ed., 2006) (DTX-275)
Lachman	Herbert A. Lieberman et al., PHARMACEUTICAL DOSAGE FORMS: TABLETS, VOL. 1 (2d. ed., 1989) (PTX-553)
Lahdenpää	Esa Lahdenpää et al., *Crushing Strength, Disintegration Time and Weight Variation of Tablets Compressed from Three Avicel® PH Grades and Their Mixtures*, 43 EURO. J. PHARMACEUTICS AND BIOPHARMACEUTICS 315 (1997) (DTX-355)
Jivraj	Mira Jivraj et al., *An Overview of the Different Excipients Useful for the Direct Compression of Tablets*, 3 PSTT 58 (2000) (DTX-344)
JTX	Joint Trial Exhibit
MSN	MSN Laboratories and MSN Pharmaceuticals
MSN Laboratories	Defendant MSN Laboratories Private Limited
MSN Pharmaceuticals	Defendant MSN Pharmaceuticals Inc.
POSA	Person of ordinary skill in the art
PTX	Plaintiff's Trial Exhibit
Swarbrick	James Swarbrick & James C. Boylan, ENCYCLOPEDIA OF PHARMACEUTICAL TECHNOLOGY (1991) (PTX-394)
USP	United States Pharmacopeia

I. INTRODUCTION

Exelixis filed this Hatch-Waxman patent infringement suit against MSN, asserting at trial claim 3 of U.S. Patent No. 11,298,349 ("the '349 patent"), which is listed in the Orange Book for Exelixis' cancer drug CABOMETYX. The '349 patent covers pharmaceutical compositions of cabozantinib (L)-malate that are essentially free of a particular genotoxic impurity and include a filler (also known as a diluent), disintegrant, lubricant, and glidant. The only disputed infringement issue is whether MSN's proposed generic version of CABOMETYX contains a glidant. The trial evidence showed it does not.

Exelixis argues that the GRASTAR granulated corn starch in MSN's tablets (i) was added to improve the formulation's powder "flow" properties and, therefore, (ii) must be considered a glidant. Exelixis is wrong on both counts.

First, MSN added GRASTAR part way through its formulation development as a diluent to adjust its tablets' disintegration and dissolution properties, not as a glidant to improve their powder flow properties. Exelixis can point to no contemporaneous evidence suggesting that MSN selected GRASTAR to address any concern about the formulation's flow. To the contrary, MSN's ANDA specifically and consistently identifies GRASTAR as a diluent. And that is not a litigation-inspired label. MSN identified the role of GRASTAR as a diluent (and that its ANDA products did not contain a glidant) in 2019, long before the asserted claims ever published in 2021. Furthermore, the *only* empirical data presented at trial confirmed that adding GRASTAR did not improve the formulation's flow properties. That Exelixis' expert initially relied on this data and then abandoned it when he discovered it did not support his infringement opinion is telling.

Second, there is no dispute that glidants can be used to improve the flow properties of a drug powder mixture. But Exelixis twists this characterization to argue that *no other* excipient can have any positive effect on powder flow without being a glidant. There is no basis in the scientific

literature for this strained interpretation, and multiple references introduced at trial refer to a diluent's positive impact on flow properties without making it a glidant. Even if GRASTAR had some effect on the flow properties of MSN's formulation—which the trial evidence showed it did not—a POSA would not conclude it is a glidant, including because there is no evidence that GRASTAR improves flow through any of the glidant mechanisms reported in the literature.

The Court should also take note that Exelixis frequently asserts that the evidence it uses to make its infringement case is "consistent" with GRASTAR being a glidant in MSN's tablets. But that does not carry Exelixis' burden of proof here. There is no question that the scientific literature says (i) certain corn starch-based excipients *can* be used as glidants; (ii) certain excipients *can* be used as glidants at concentrations of less than 10%; (iii) glidants *can* be added at the pre-lubrication stage of tablet manufacturing; and so on. But the same would be true if the word "glidants" was replaced with "diluents" (or even other types of excipients). Exelixis cannot rely on generic literature statements about the *potential* uses of broad categories of excipients, particularly when they do not differentiate one excipient from another, to prevail.

Given the dearth of supporting evidence, Exelixis engages in trial by snippet. They point to one MSN document that—consistent with the literature—notes that starch-based excipients *can* be used as a glidant (or a diluent, or a binder) and two statements from MSN's ANDA that GRASTAR plays a role in the overall flow properties of MSN's formulation. But those statements, which documents and sworn percipient witness testimony confirmed were based on the scientific literature and not any flow property testing on MSN's formulation, also expressly identify GRASTAR as a diluent in MSN's formulation and certainly do not prove it is a glidant.

As explained in detail below and in MSN's proposed findings of fact, Exelixis failed to meet its burden of showing that MSN will directly or indirectly infringe claim 3 of the '349 patent.

II. BACKGROUND

A. The asserted claim

Claim 3 of the '349 patent claims "[a] pharmaceutical composition for oral administration comprising [cabozantinib (L)-malate] one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition; and wherein the pharmaceutical composition is essentially free of 6,7-dimethoxy-quinoline-4-ol." DFF ¶ 5. The only disputed infringement issue at trial was whether MSN's tablets contain a glidant.

B. Methods to improve powder flow

Each ingredient has its own flow properties and contributes to a powder mixture's overall flow properties. DFF ¶ 227. Several methods are available to improve flow of a powder blend, if necessary. DFF ¶ 229. For instance, granulation techniques can be used to form aggregates of API and other powder ingredients that are more uniform in size and shape and, therefore, flow better than the individual components combined. DFF ¶ 230. Certain excipients may also be added to the formulation to create the desired flow properties. DFF ¶¶ 231-232.

C. Glidants and diluents

The parties agree that glidants can be added to a formulation to improve the flow properties of a drug powder mixture. DFF ¶ 232; PFF ¶ 19. They disagree whether a POSA would consider *every* ingredient in a formulation to be a glidant if it has *some* positive impact on the powder blend's overall flow properties. *See* DFF ¶ 255; Tr. 128:25-129:2, 131:23-132:8 (Koleng).

No scientific literature states that a glidant is the *only* excipient that can have a positive effect on a powder mixture's flow. DFF ¶ 255. Or that every excipient that does is a glidant. *Id.* Indeed, one common textbook definition (Ansel) describes diluents as "[i]nert substances used as fillers to create the desired bulk, *flow properties*, and compression characteristics in the preparation

of tablets and capsules." DFF ¶ 231. A diluent can improve flow of a powder blend by bulking up the mixture, reducing the chance of poorly flowing API and other excipients interacting. *Id.* By contrast, a POSA understands that glidants can improve flow of a powder blend through five mechanisms widely reported in the scientific literature: (1) coating/adherence; (2) adsorbing fine particles; (3) reducing electrostatic forces; (4) adsorbing environmental gases; and (5) reducing van der Waals forces. DFF ¶ 232.

III. LEGAL STANDARD

"The patent owner has the burden of proving infringement and must meet its burden by a preponderance of the evidence." *Takeda Pharm. Co. v. Teva Pharm. USA, Inc.*, 668 F. Supp. 2d 614, 619 (D. Del. 2009); *see also Vanda Pharm. Inc. v. WestWard Pharm. Int'l Ltd.*, 887 F.3d 1117, 1125 (Fed. Cir. 2018). This burden never shifts to the defendant. *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008) (also noting that "the risk of decisional uncertainty stays on the proponent of the proposition"). A patentee may prove infringement with circumstantial evidence, but that does not permit a patentee to rely on speculation. *See Largan Precision Co., Ltd. v. Genius Elec. Optical Co., Ltd.*, 646 F. App'x 946 (Fed. Cir. 2016).

Induced infringement requires a showing that the alleged infringer knew of the patent, knowingly induced the infringing acts, and possessed a specific intent to encourage another's infringement of the patent. *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1328 (Fed. Cir. 2009). The mere knowledge of possible infringement will not suffice to establish intent. *Id.*

IV. ARGUMENT

A. MSN added GRASTAR as a diluent, not a glidant.

MSN laboratory notebooks, reports, development documents, and percipient witness testimony tell the same consistent story: MSN added GRASTAR as a diluent in its tablets, not a glidant. The trial evidence confirmed that MSN never even considered adding a glidant to its

formulation. There was no reason to do so. MSN resolved any concern with its API's poor flow properties through wet granulation. And subsequent excipient changes, including GRASTAR's addition, were focused on matching the disintegration and dissolution profile of the brand product, not improving flow properties. Importantly, the only empirical data confirms that the addition of GRASTAR did nothing to improve the formulation's flow properties. As MSN reported to FDA, GRASTAR is a diluent in MSN's formulation.

1. MSN used wet granulation to improve the API's flow properties.

There is no dispute that cabozantinib (L)-malate has poor flow properties. PFF ¶ 23; Br. at 6-7. But that does not suggest, as Exelixis argues, that a glidant was needed—much less used—in MSN's formulation. There are multiple ways to improve the flow properties of a poorly flowing API. DFF ¶ 229. Here, MSN's product development report explicitly identifies the method MSN used to improve the API's flow properties: wet granulation. DFF ¶ 242. There is no dispute that this manufacturing technique can resolve an API's poor flow. DFF ¶ 230. And Dr. Koleng *agreed* that MSN's use of wet granulation *did*, in fact, improve the formulation's flowability. DFF ¶ 243.

The trial evidence further confirmed that the use of wet granulation fully resolved any issue with the API's poor flow properties. *Id.* Exelixis cannot identify any subsequent expression of concern in MSN's development documents suggesting additional steps were needed to further improve flow. *Id.* Nor were there any experiments performed, testing conducted, or formulation changes considered with any specified goal of further improving flow properties. *Id.* That there is no contemporaneous evidence suggesting MSN tested, debated, or even considered the need for a glidant during development is telling.

This leaves Exelixis only with the general undisputed proposition that glidants "may" be added to formulations with poorly flowing API. Br. at 7. But the trial evidence confirmed that is not why GRASTAR was added to MSN's formulation, nor the function it is serving here.

2. GRASTAR was added as a diluent to adjust disintegration and dissolution properties.

MSN laboratory notebooks, reports, and other documents show that MSN's excipient changes during formulation development, including the addition of GRASTAR as a diluent, were focused on the tablets' disintegration and dissolution properties, with the explicit goal of matching the brand product's profile. DFF ¶¶ 245-248.

Take MSN's laboratory notebooks, which both sides' experts reviewed and relied upon when forming their infringement opinions, and which confirm that MSN was focused on the tablet's disintegration and dissolution profile when it added GRASTAR. DFF ¶¶ 244, 246. Of course, it makes sense to look to the laboratory notebooks to understand why MSN added GRASTAR. Laboratory notebooks can serve as important contemporaneous evidence describing drug product development. *See, e.g.*, *Trovan Ltd. v. Sokymat SA*, 299 F.3d 1292, 1302 (Fed. Cir. 2002) ("corroboration preferably comes in the form of physical records that were made contemporaneously" with the invention); *Sandt Tech., Ltd. v. Resco Metal and Plastics Corp.*, 264 F.3d 1344, 1350-51 (Fed. Cir. 2001) ("Documentary or physical evidence that is made contemporaneously with the inventive process provides the most reliable proof that the inventor's testimony has been corroborated").

But Dr. Koleng completely ignored MSN's notebooks at trial (Tr. 129:5-8), likely because they do not support Exelixis' claims. As Dr. Donovan testified, the notebooks show that when MSN first substituted granulated GRASTAR in place of unmodified corn starch during development, MSN was focused on adjusting the formulation's disintegration and dissolution properties. DFF ¶¶ 245-246. It is not surprising MSN selected GRASTAR for that purpose—the manufacturer itself touts the filler's "excellent" disintegration properties. DFF ¶ 238. Dr. Donovan gave unrebutted testimony that there is simply no indication in MSN's laboratory notebooks that

MSN added GRASTAR to improve powder flow properties. DFF ¶ 249.[1]

Subsequent excipient adjustments and optimization testing confirm that MSN was focused on the disintegration and dissolution properties of its tablets during formulation development. After MSN added GRASTAR to the formulation, it also evaluated and adjusted the amount of the intra-granular disintegrant, croscarmellose sodium, that would produce a similar dissolution profile to the brand product. DFF ¶ 247. MSN then evaluated whether adjusting the amounts of several other excipients, including GRASTAR, would better match the brand's dissolution profile. DFF ¶¶ 247-248. There is no comparative data or analysis showing that any of these adjustments affected the prototypes' flow properties. DTX-215.38-63. Indeed, Exelixis presented no evidence at all that flow properties were a consideration in performing these comparative experiments.

Exelixis argues that "MSN's own data" shows that GRASTAR could not have been added to adjust disintegration and dissolution properties, because MSN ultimately found there were "no significant difference[s]" in the dissolution profiles of prototype batches with 6.7%, 9.7%, and 12.7% GRASTAR. DFF ¶ 248. But the fact this explicitly named "comparative *dissolution*" testing was performed at all proves MSN's point. DTX-215.60. GRASTAR was added and then the amount evaluated to produce the closest disintegration and dissolution profile to the brand product. DFF ¶¶ 246, 248. A POSA certainly would not conclude from these comparative results that GRASTAR has *no* effect on the formulation's dissolution profile. DFF ¶ 248. Rather, there is simply no significant difference in the prototypes' dissolution within the range of GRASTAR amounts tested. *Id.* This says nothing about what the dissolution profile would be *without*

[1] Dr. Koleng testified that he did not rely on any "data" from MSN's laboratory notebooks at trial because of a calculation error identified on one page. Tr. 107:1-19 (Koleng). *See infra* at 8-11. But he also did not identify any experiments, statements, or other evidence from anywhere in MSN's notebooks suggesting MSN added GRASTAR to improve powder flow properties.

GRASTAR. *Id.* Nor does it suggest anything about how the dissolution profile of a formulation with GRASTAR would compare to a prototype with unmodified corn starch, which was MSN's initial choice for extra-granular diluent. This "comparative dissolution" testing provides no evidence to support Exelixis' contention that GRASTAR is being used as a glidant.

3. MSN's ANDA identifies GRASTAR as a diluent.

In its ANDA, MSN was required to tell FDA: "What is the function of each excipient?" DTX-231.2. There is no dispute that MSN's ANDA consistently identifies GRASTAR's function as a diluent. DFF ¶ 234. MSN was also required to identify "differences between [MSN's] formulation and [CABOMETYX]." DTX-231.4. Again, MSN told FDA that CABOMETYX contains a glidant, and MSN's tablets do not. *Id.* And Exelixis cannot suggest MSN's classification of GRASTAR was self-serving for litigation. MSN developed its formulation and identified the role of GRASTAR as a diluent (and that its ANDA products did not contain a glidant) in 2019, long before the asserted claims ever published in 2021. DFF ¶ 233.

4. Testing data shows the addition of GRASTAR did not improve flow.

Exelixis did not present *any* experimental or testing data establishing that flow properties improved when MSN added GRASTAR to its formulation. To the contrary, the *only* empirical data introduced at trial shows that GRASTAR's addition did *not* actually improve the flow properties of MSN's formulation. And Dr. Koleng's initial reliance on—and then abandonment of—MSN's testing data when it did not support his infringement opinion is revealing.

During formulation development, MSN initially used 30 mg of unmodified corn starch (maize starch B) in the extra-granular layer of its tablet formulation, as seen in prototype Batch No. 252/023. DFF ¶ 245. MSN later replaced maize starch B with 30 mg of GRASTAR granulated corn starch, as seen in prototype Batch No. 252/044. *Id.* There were no other differences between the formulations of these two batches, as seen below:

Batch No. 252/023		Batch No.252/044	
Ingredients	**Mg/Unit**	**Ingredients**	**Mg/Unit**
Cabozantinib (L)-malate	76.02 (78.31)	Cabozantinib (L)-malate	76.02 (78.08)
Corn starch	84.00 (81.71)	Corn starch	84.00 (81.94)
Lactose monohydrate	82.98	Lactose monohydrate	82.98
Croscarmellose sodium	9.00	Croscarmellose sodium	9.00
Hydroxy propyl cellulose	6.00	Hydroxy propyl cellulose	6.00
Purified Water	qs	Purified Water	qs
Corn starch	30.00	Granulated corn starch	30.00
Croscarmellose sodium	9.00	Croscarmellose sodium	9.00
Magnesium Stearate	3.00	Magnesium Stearate	3.00
Opadry yellow	9.00	Opadry yellow	9.00
Purified water	qs	Purified water	qs
Bulk density	0.515 g/mL	Bulk density	0.541
Tapped density	0.708	Tapped density	0.825
Carr index	27.7	Carr index	25.92
H.R.	1.375	H.R.	1.350

Id.; DDX(Koleng)-2. MSN experimentally measured the bulk and tapped density of the powder blend for these two batches and recorded the measurements in its notebook, as seen above. DFF ¶ 250. From those measurements, the sample's Hausner ratio and Carr Index—two common methods used to characterize powder flow—can be calculated. DFF ¶ 228.

An MSN scientist performed that calculation for these batches and recorded the resulting values in the notebook, also reflected above. DFF ¶ 250. Dr. Donovan explained that a POSA would not consider such minimal variations in Hausner ratio and Carr Index to reflect any meaningful improvement in flow properties for the batch with GRASTAR compared to the batch with maize starch B. DFF ¶ 249. Indeed, the USP would characterize the flow character for both batches as "poor," based on the values that were recorded in the notebook. Tr. 137:5-16 (Koleng).

Nevertheless, Dr. Koleng originally opined that the data showed a meaningful reduction (where a lower number signifies better flow) in the recorded Hausner ratio and Carr Index values (i.e., that the sample with GRASTAR had better flow than the sample with maize starch B). Tr. 137:17-21. Because, according to Dr. Koleng, there is *no* minimum magnitude of change in Hausner ratio or Carr Index required to reflect a meaningful difference in a powder's flow

character. Tr. 131:23-132:8, 147:15-25. For example, if sample A's Carr Index was 27.7, and sample B's Carr Index was 27.6, Dr. Koleng would conclude sample B shows an improvement in flow. Tr. 132:3-8. Following the analytical framework he applies, that means a glidant must have been added to sample B. Tr. 128:25-129:2. In forming his infringement opinion, he relied on the purported (marginal) "directional reduction" of Hausner ratio and Carr Index when GRASTAR replaced maize starch B in MSN's formulation to support his opinion that GRASTAR improved flow and was a glidant. Tr. 137:22-138:25. In fact, it was "one of the pillars" of, and "important" to, his opinion that GRASTAR is functioning as a glidant. *Id.*

But the MSN scientist made a calculation error when he recorded the Hausner ratio and Carr Index values for Batch No. 252/044. DFF ¶ 252. On cross-examination, Dr. Koleng conceded that, using the measured bulk and tapped density values recorded for the batches, the correctly calculated Hausner ratio and Carr Index are:

Batch No. 252/023		Batch No.252/044	
Bulk density	0.515 g/mL	Bulk density	0.541
Tapped density	0.708	Tapped density	0.825
Carr index	27.7	Carr index	~~[illegible]~~ 34.42
H.R.	1.375	H.R.	~~[illegible]~~ 1.52

Id.; DDX(Koleng)-4. Dr. Koleng also agreed that the correctly calculated Hausner ratio and Carr Index for the prototype with GRASTAR was higher than the prototype with maize starch B—indicating a decrease in flowability when GRASTAR was added. Tr. 140:10-19; DFF ¶ 253.

Exelixis and Dr. Koleng now argue that MSN's notebook is unreliable and should be disregarded completely, because it contains an "error of unidentified origin." Br. at 10; Tr. 107:12-19. But the error's origin *was* identified. Exelixis introduced no evidence to cast doubt on the experimentally *measured* bulk and tapped density values that the MSN scientist recorded for these batches. Rather, the error was in a simple mathematical *calculation*—one Dr. Koleng has performed many times in his career—that generates the Hausner ratio and Carr Index based on a

sample's measured densities. DFF ¶ 228; Tr. 131:8-10 (Koleng).

The reason Dr. Koleng gave for ignoring this data at trial was that the corrected Hausner ratio and Carr Index values were based on "unverified" bulk and tapped density measurements. Tr. 140:13-19. What he meant by "unverified" was not explained; despite Exelixis' burden of proof, Dr. Koleng chose not to do any of his own testing on MSN samples. Tr. 108:7-9. But of course, he had no problem relying on "unverified" density measurements taken by MSN when he thought the resulting Hausner ratio and Carr Index calculations *supported* his opinion. DFF ¶ 244. He cannot renounce that data now that it shows GRASTAR's addition did not improve the flow properties of MSN's tablets.

Exelixis' last pitch for discounting MSN's testing data is that, "even if credited," it would "simply show that GRASTAR … is not as effective a glidant as unmodified corn starch, another well-documented glidant." Br. at 11. But Dr. Koleng explicitly *disclaimed* any opinion that maize starch B functioned as a glidant in Batch No. 252/023. DFF ¶ 254. And there is no dispute that unmodified corn starch—like pregelatinized corn starch—can function as a filler or a disintegrant without being a glidant. Tr. 155:7-13, 155:22-156:15 (Koleng). As such, there is absolutely no evidence in the trial record that Batch No. 252/023 included a glidant. So, the fact that Batch No. 252/044 (with GRASTAR) had worse flow than a batch *without a glidant* cannot possibly prove that GRASTAR improved flow and functions as a glidant in MSN's tablets.

MSN's flow property testing data was one of the "pillars" of Dr. Koleng's opinions when he thought it supported infringement. Exelixis cannot now deny what it shows: the *only* empirical data presented at trial proves that the addition of GRASTAR did not improve the flow properties of MSN's formulation.

B. A POSA would not understand GRASTAR to be a glidant in MSN's tablets.

Even without empirical data, a POSA would not understand GRASTAR to be a glidant in

MSN's tablets. Exelixis has not identified any MSN or other document ever referring to GRASTAR as a glidant. And the same evidence Exelixis says "supports the conclusion" that GRASTAR is a glidant could be equally used to "support the conclusion" it is a diluent; therefore, it does nothing to prove GRASTAR is a glidant in MSN's tablets.

1. MSN documents and scientific literature do not describe GRASTAR as a glidant.

Exelixis claims that "MSN repeatedly told the FDA that GRASTAR was a known glidant." Br. at 11. Not so. At trial, Exelixis did not present a single MSN document or percipient witness testimony ever describing GRASTAR as a glidant. To the contrary, MSN repeatedly and unequivocally identified GRASTAR as a diluent in its tablets. DFF ¶ 234; *see supra* at 8.

Nor did Exelixis present any other documents referring to GRASTAR as a glidant. In fact, the GRASTAR manufacturer's technical data sheet identifies several potential functions for the ingredient, including filler, binder, and disintegrant—but not glidant. DFF ¶ 237. The manufacturer notes that GRASTAR has "good flowability,"[2] but this does not suggest it is a glidant either. DFF ¶ 238. Indeed, the scientific literature confirms that formulators often consider a filler's flow properties when selecting it for use as a filler in a formulation—without it being considered a glidant. *See infra* at 15-16.

Lacking any documents describing GRASTAR as a glidant, Exelixis relies on scientific literature *generally* describing *possible* uses of unmodified corn starch and pregelatinized corn starch in pharmaceutical formulations. *See*, *e.g.*, Br. at 8. But even if the Court accepts that these

[2] Dr. Koleng agreed that some grades of pregelatinized starch have been rendered more flowable than their unmodified versions. Tr. 156:21-24. And that there are many different types and grades of starches that can have different properties, including flow properties. Tr. 155:14-21.

references provide any guidance on GRASTAR's possible functions—which it should not[3]—they would do nothing to move the ball on Exelixis' infringement claims. These broad categories of starch-based excipients are also undisputedly described in the literature as potential diluents, binders, and disintegrants, among other things. DFF ¶¶ 235, 239. Exelixis' references provide no insight on which of these functions GRASTAR is serving in the MSN formulation at issue here.

Exelixis similarly relies on one MSN document that makes a generalized statement about the potential use of starch-based excipients in pharmaceutics. MSN's Justification for Microbial Method Validation document states that "[s]tarch are used in pharmaceutical industry for a wide variety of reasons, such as an excipient in tablet and capsule as a diluent, as a glidant *or* as a binder." DFF ¶ 269. Of course, this is another true statement about how certain starch-based ingredients *may* be used in formulations. *Id.* But it says nothing about how GRASTAR functions in MSN's tablets at issue. *Id.* Certainly, Exelixis does not claim that all starch-based ingredients (including GRASTAR, here) serve as diluents, as glidants, *and* as binders in every formulation in which they are used.

Dr. Koleng concedes that both unmodified and pregelatinized starches can serve as fillers in pharmaceutical formulations without also being glidants. Tr. 155:7-156:15. Thus, at the *very most*, the documents and scientific literature introduced by Exelixis shows only that GRASTAR *could* potentially serve as a filler, a binder, a disintegrant, or glidant, depending on the

[3] A POSA would not consider scientific references discussing the properties or functions of unmodified starches to apply to pregelatinized starches. Tr. 207:6-9 (Donovan). Unmodified and pregelatinized starches have different properties, and they are categorized separately in the scientific literature. *See* Tr. 156:16-20 (Koleng); Tr. 204:2-4 (Donovan); DTX-275.748, 754. And while Exelixis found two decades-old sources—one textbook and one patent—listing pregelatinized starch as a potential glidant (among other possible functions), Dr. Koleng did not identify *any* examples of *any* formulation in which pregelatinized starch has ever actually served as a glidant. DFF ¶¶ 240-241; *see also* Tr. 208:7-9 (Donovan).

formulation. That does not satisfy Exelixis' burden to prove infringement.

2. The manufacturing stage and concentration at which GRASTAR is added does not prove it is a glidant.

Exelixis also argues that the stage and concentration at which GRASTAR is added during MSN's manufacturing process is "consistent" with that of a glidant. Br. at 7. That proves nothing. Other excipients, *including* fillers, undisputedly can be added at the same stage and concentration. These facts thus shed no light on GRASTAR's function in MSN's tablets either.

Specifically, GRASTAR is added to the MSN powder blend after wet granulation, at the pre-lubrication stage of manufacturing. PFF ¶ 30. But both sides' experts agree that disintegrants (including croscarmellose sodium in MSN's tablets), fillers, and many other ingredients can also be added at the same stage. DFF ¶ 268. The fact GRASTAR is added during pre-lubrication does nothing to identify its potential function in MSN's tablets. *Id.*

Nor does the 9.71% concentration at which GRASTAR is used in MSN's tablets prove its function. Exelixis argues that amount of a corn starch-based excipient is "consistent" with its use as a potential glidant (barely, at a range of 10% or less). Br. at 10. But that concentration is also "consistent" with many other ingredients, including diluents and disintegrants. DFF ¶ 235. As Dr. Donovan explained, "diluents are used in a wide variety of concentrations, as low as a couple percent up to maybe as high as 75, 80, 90 percent even." Tr. 201:21-202:4. Dr. Koleng did not dispute this fact about the way diluents can be used in pharmaceutical formulations, which is reported in the scientific literature. DFF ¶ 235.

If anything, the GRASTAR concentrations MSN considered during formulation development suggest it is *not* functioning as a glidant in MSN's tablets. During optimization trials, MSN evaluated the dissolution profile of prototypes containing GRASTAR at concentrations of 6.7%, 9.7%, and 12.7% (which is outside Exelixis' range for purported glidant use). DFF ¶ 248.

While MSN ultimately chose the middle concentration for its final tablets, there were no significant differences in the prototypes' dissolution profiles. *Id.* Following Exelixis' strained reasoning, GRASTAR would have functioned as a glidant in the prototype with 9.7% GRASTAR, but not in the prototype with 12.7% GRASTAR,[4] even though they produced the same dissolution profile.

Once again, Exelixis is left only with undisputed generalized propositions that glidants "may" be added to formulations during the pre-lubrication stage and at concentrations up to 10%. Br. at 7-8. But this does nothing to prove GRASTAR is a glidant in MSN's formulation.

C. Even if GRASTAR improved the flow properties of MSN's tablets, that would not make it a glidant.

Exelixis has failed to establish that the addition of GRASTAR actually improved flow properties in MSN's formulation. But even if it did, that would not prove infringement. Exelixis' entire case rests on a false premise, because glidants are not the only excipient that can impact a powder mixture's flow properties. And a POSA would not automatically characterize every excipient that has a positive impact on a formulation's flowability to be a glidant.

1. Diluents can have a positive impact on overall powder flow properties.

The parties agree that glidants can be used to improve the flow properties of a drug powder mixture. DFF ¶ 232; PFF ¶ 19. But Exelixis presented no evidence that the converse is automatically true. As Dr. Donovan explained, a POSA would not consider *every* excipient that has any positive impact on a formulation's powder flow properties, no matter its identity or amount, to be a glidant. DFF ¶ 255. Certainly, no reference was presented at trial stating that a glidant is the *only* excipient that can have a positive effect on a powder mixture's flow. *Id.* Or that every excipient that does is a glidant. *Id.*

[4] According to Exelixis' reference, starch-based glidants used in amounts in excess of 10% "can retard flow rates." PTX-394.44.

To the contrary, scientific literature provides guidance on how the selection of a filler (without also being a glidant) can affect the overall flow properties of a powder mixture. DFF ¶ 256. For example, Lahdenpää describes various tablet characteristics, including flow properties, for three different grades of microcrystalline cellulose, a frequently used filler. DFF ¶¶ 257. Dr. Koleng admitted that he, too, has used MCC as a filler, but never as a glidant in any of the hundreds of formulations he has helped prepare. *Id.* Nor do the authors call any grade of MCC a glidant—even the one they measured to have good flow properties. *Id.*; DTX-355.1, 6.

Similarly, Jivraj reports on the functionality of certain fillers. DFF ¶ 258. Jivraj states that MCC's "limitation of poor flow can be offset by mixing with *another filler* with good flowability, such as α-lactose monohydrate." *Id.* Once again, Dr. Koleng conceded that lactose is a common diluent, but he has never used it as a glidant in any formulation. *Id.* Jivraj's report on granulated lactitol is even more revealing: that filler has "good flow properties, and formulations containing granulated lactitol do not require a glidant." *Id.* Like granulated lactitol, it is undisputed that GRASTAR has "good flowability." DFF ¶ 238. When combined with the other ingredients in MSN's tablets, there is simply no evidence that a glidant was required to improve the formulation's flow properties. DFF ¶¶ 243, 249.

Dr. Koleng's interpretation of the plain and ordinary meaning of a glidant also falls apart when taken to its logical end. He testified that any excipient that produces a "directional improvement in flow" is a glidant, with no evaluation of whether the change in flow character of a powder mixture is meaningful or how it is accomplished. Tr. 128:25-129:2, 131:23-132:8. But Dr. Koleng provided no literature support for the proposition that a POSA would identify an excipient to be a glidant if its addition shifts the Carr Index of a formulation from, for example, 27.7 to 27.6. Tr. 131:23-132:2. Every ingredient has its own flow properties, which will necessarily

have some impact on the powder mixture's overall flow properties when added. DFF ¶ 227. Using Dr. Koleng's analytical framework, every single excipient—whether it is a disintegrant, lubricant, binder, or anything else—whose individual flow properties are better than the powder mixture's without that excipient would automatically be labeled a glidant. One might expect that at least half—if not all—of the excipients added to a formulation with poorly flowing API could be deemed to be a glidant if Dr. Koleng's rigid interpretation is applied. Exelixis presented no support in the literature for such an extreme understanding of "glidant," which is directly contradicted by references such as Ansel, Lahdenpää, and Jivraj.

2. There is no evidence GRASTAR improves flow in MSN's tablets through any reported glidant mechanism.

The scientific literature consistently describes five different ways in which glidants operate to improve the flow properties of a drug powder mixture: (1) coating/adherence; (2) adsorbing fine particles; (3) reducing electrostatic forces; (4) adsorbing environmental gases; and (5) reducing van der Waals forces. DFF ¶ 232. These are not additional unconstrued "proof requirements," as Exelixis argues (Br. at 13-14), but rather evidence to corroborate whether an excipient is a glidant in a specific formulation (DFF ¶¶ 260, 262, 265-267).

At trial, Dr. Donovan explained that there was no evidence GRASTAR operates through any of these five mechanisms to improve flow in MSN's tablets. DFF ¶ 259. Faced with rebutting her analysis, Dr. Koleng extended his opinions beyond credibility by testifying that it was more likely than not GRASTAR improved flow properties through not one but *all five* of these very disparate mechanisms. Tr. 166:2-6, 167:1-5, 169:21-170:2, 170:11-15, 170:24-171:3 (Koleng). But his *ipse dixit* analysis does not stand up to scrutiny.

For example, the most common glidant mechanism is improving flow by coating or adhering to the surface of larger host particles, which reduces friction between them. DFF ¶ 260.

Colloidal silicon dioxide, with submicroscopic particles of about 15 nanometers,[5] is the most common example and is used at concentrations of less than 1%.[6] *See* PTX-572A.13; PTX-394.44; Tr. 173:7-12, 175:2-12 (Koleng). GRASTAR, on the other hand, cannot possibly coat the surface of particles in MSN's powder blend. ¶ DFF 261. GRASTAR's average particle size is undisputedly 81.58 microns—over 5,000 times larger than colloidal silicon dioxide—and the granules of API and other intra-granular components in MSN's formulation are approximately 150 microns. DFF ¶ 261. As Dr. Donovan explained, with her demonstrative, "there isn't a physical way for an 80-micron particle to decorate the surface of [a] 150-micron particle, one that's only twice its size such that it acts in the way a glidant acts." Tr. 219:9-12; *see also* DDX(Donovan)-11.

Similarly, GRASTAR cannot possibly adsorb "fine" particles in MSN's formulation, as Dr. Koleng claims, because of their comparable sizes. DFF ¶ 263. All Dr. Koleng could establish at trial was that the particles he characterized as "fines" were less than 150 microns. *Id.* But he presented no evidence that the purported "fines" were smaller than the size of GRASTAR, much less small enough to be adsorbed by GRASTAR. *Id.*; DDX(Donovan)-12.[7] His opinions that GRASTAR improved flow properties through the other three glidant mechanisms were similarly devoid of any supporting evidence: no indication of powder sticking that would require a glidant to disperse electrostatic charge; no evidence of gas buildup in the powder blend that would require a glidant to adsorb gases; and no evidence of particles in the powder blend small enough to create van der Waals forces requiring a glidant to reduce them. DFF ¶¶ 265-267.

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[5] 15 nm (nanometers) is equal to 0.015µ (microns).

[6] All of the '349 patent's glidant examples are colloidal silicone dioxide or fumed silica used at less than 1% concentrations. JTX-0004.6-7; Tr. 175:13-17 (Koleng).

[7] By contrast, the GRASTAR manufacturer hypothesized that much smaller micronized fenofibrate particles (less than 10 microns) could potentially adhere to GRASTAR. DFF ¶ 264. But that bears no relevance to the purported "fines" here, which are up to over 15 times larger. DFF ¶ 263.

D. Out-of-context statements in MSN's product development report do not prove GRASTAR is a glidant in MSN's tablets.

Based on literature describing the "good flowability" of GRASTAR, MSN reasonably expected that its addition could positively impact the overall flow properties of its tablets before formulation development began. DFF ¶¶ 238, 270; PFF ¶ 27. This is reflected in MSN's product development report describing the "important role" GRASTAR has on flow characteristics. Exelixis' infringement case relies heavily on these statements, but they neither state nor suggest—much less prove—that GRASTAR functions as a glidant in MSN's formulation.

Specifically, in the "Initial Risk Assessment" of its product development report, MSN prepared a table describing the proposed ingredients for its ANDA products. DFF ¶ 270. An initial risk assessment is performed *before* formulation development starts to direct and prioritize what should be evaluated for a formulation. *Id.* Indeed, the table appears before MSN's report on its formulation development studies. DTX-215.34; Tr. 144:17-22 (Koleng). In its initial assessment,[8] MSN stated that GRASTAR "is ***used as a diluent*** in minimal concentration" and further expected (as this statement was written before formulation trials were done) that it also "enhances the flowability of the granules." DFF ¶ 270; DTX-215.36. But this statement does not prove the ingredient is a glidant, as Exelixis claims.

First, as discussed above, glidants are not the only excipients that can have a positive impact on the overall flow properties of a powder mixture. *See supra* at 15-17. The very table Exelixis relies upon confirms this. In it, MSN also stated that the magnesium stearate in MSN's formulation "enhances the flow properties." DFF ¶ 271. Dr. Koleng agreed that magnesium stearate is a lubricant in MSN's formulation and did not claim it was a glidant. *Id.* MSN also stated

[8] This initial risk assessment also follows the section characterizing the excipients, where GRASTAR is identified as a diluent (DTX-215.28) and noted to be "manufactured by Japan Corn Starch Co. Ltd." and "used as a diluent in the formulation" (DTX-215.29).

that the lactose monohydrate in MSN's formulation "can impact the flow properties of the blend." *Id.* Again, Dr. Koleng agreed that lactose monohydrate is a diluent in MSN's formulation and did not claim it was a glidant. *Id.* These concessions undermine his results-oriented characterization of GRASTAR as a glidant based on precisely the same evidence. Thus, MSN's "initial risk assessment" expectation that GRASTAR could have a positive impact on the overall flow properties of its formulation is not an "admission" that it is a glidant in its final tablets.

Second, despite MSN's initial expectation, there was no evidence presented at trial showing that GRASTAR actually improved the flow properties of this formulation in any—much less a meaningful—way. The only empirical data shows that there was no ultimate improvement in flow character when GRASTAR was added. *See supra* at 8-11. Mr. Nithiyanandam testified that, consistent with an "initial" risk assessment, MSN's statement was written based on the scientific literature, before formulation experiments were initiated or completed. DFF ¶ 270.[9]

Similarly, Exelixis relies (heavily, quoting it five times) on the section titled "Optimization of level of Granulated Corn Starch ***(Diluent)***," where MSN stated—again after explicitly identifying it as a "diluent"—that "[t]he level of Granulated corn Starch plays an important role in flow characteristics." Br. at 9. Setting aside that this statement does not indicate GRASTAR is a glidant, Mr. Nithiyanandam explained that it, too, was based on the scientific literature. Tr. 62:21-64:5. Exelixis cites a truncated portion of Mr. Nithiyanandam's testimony to suggest "this statement [about flow] was based on studies done by MSN." Br. at 9. But once Exelixis' counsel

[9] Dr. Koleng simply discredits the only sworn percipient witness testimony about this document. Tr. 143:23-144:16 (Koleng). Exelixis also argues that Mr. Nithiyanandam's explanation cannot be "reconciled" with the plain language of the product development report because MSN's expert agreed it "summarizes the development of MSN's ANDA products." Br. at 11. But this makes no sense. As part of its product development—at the *beginning*—MSN performs an initial risk assessment of formulation variables based on the scientific literature. DFF ¶ 270.

permitted him to read the rest of the section, Mr. Nithiyanandam explained that the optimization trial was conducted to evaluate the dissolution properties of prototypes with varying amounts (6.7%, 9.7%, and 12.7%) of GRASTAR. Tr. 62:21-64:5, 64:16-19 (Nithiyanandam); DTX-215.58-60; DFF ¶ 248. Contrary to Exelixis' insinuation, there is no evidence of flow property testing on the three batches described in this *dissolution* optimization trial. And there certainly is not any data showing that flow improved as the amount of GRASTAR in the prototypes increased.

Because the statements Exelixis relies upon in MSN's product development report are not "representations" to FDA that GRASTAR is a glidant, the cases they cite also do not help them. Br. at 11. In *Intendis GmbH v. Glenmark Pharmaceuticals, Inc. USA.*, the court found a claim requiring the penetration enhancers triglyceride and lecithin infringed under the doctrine of equivalents when the defendant repeatedly referred to the isopropyl myristate in its formulation as a "penetration enhancer" selected to replace the triglyceride and lecithin in the brand product. 822 F.3d 1355, 1361-63 (Fed. Cir. 2016). There is no evidence here that MSN considered GRASTAR as a replacement to the colloidal silicon dioxide glidant in CABOMETYX, much less that it ever considered or called GRASTAR a "glidant."

The court's holding in *Vifor Fresenius Med. Care Renal Pharm. v. Teva Pharms. USA*, 623 F. Supp. 3d 389 (D. Del. 2022) actually highlights the proof that is missing from Exelixis' case. In *Vifor*, the court found a claim requiring that iron oxy-hydroxide in a composition be "essentially non-bioabsorbale" infringed by the defendant's ANDA product. *Id.* at 414-16. The court relied on defendant's product development report,[10] which stated that the ANDA product's iron is "not available in soluble form to be absorbed in the [GI tract]." *Id.* at 415. This statement was based on

[10] The court also relied on statements from the defendant's label that were copied, pursuant to FDA regulations, from the brand's label. *Vifor*, 632 F. Supp. 3d at 415. But that presents no parallel to this case.

reported underlying dissolution studies that appeared to be the defendant's "own work." *Id*. By contrast, here, there is *no* underlying data showing the addition of GRASTAR actually improved the flow properties of MSN's formulation.[11] *See supra* at 8-11.

As the Federal Circuit has held: "In some cases, the ANDA specification directly resolves the infringement question because it defines a proposed generic product in a manner that either meets the limitations of an asserted patent claim or is outside the scope of such a claim ... [but] in cases in which the ANDA specification does not resolve the infringement question in the first instance, we have endorsed the district court's reference to relevant evidence, including biobatch data and actual samples of the proposed generic composition that the ANDA filer had submitted to the FDA." *Ferring v. Watson*, 764 F.3d 1401, 1408-09 (Fed. Cir. 2014). There is no question that MSN's specification does not prove there is a glidant in MSN's tablets. Nor does the rest of the evidence Exelixis introduced at trial.

To try and carry its burden of proving infringement, Exelixis presented: (1) literature and one MSN document saying some corn starch-based excipients *can* be used as glidants (or can be used as fillers or other ingredients); (ii) literature saying some corn starch-based excipients *can* be used as glidants at concentrations of less than 10% (or can be used as fillers or other ingredients at that concentration); (iii) expert testimony that glidants (or fillers or other ingredients) *can* be added at the pre-lubrication stage of tablet manufacturing; and (iv) two snippets from MSN's product development report, which Exelixis interprets as admissions that GRASTAR improves the flow of MSN's formulation (notwithstanding empirical data undermining the claim). And Exelixis'

[11] For the same reason, Exelixis' citation to *Reckitt Benckiser Pharm. v. Watson Labs. et al*, 2016 WL 3186659 (D. Del.), is inapposite. In that case, this court found an asserted patent's viscosity claim limitation infringed based on the defendant's reported *data* showing its ANDA product's viscosity was within the preferred range disclosed in the patent. *Id.* at *19-20.

interpretation of those two MSN statements is only *potentially* relevant if the Court accepts—which it should not—Exelixis' strained understanding that a glidant is the *only* excipient that can have a positive effect on a powder mixture's flow, or that every excipient that does is a glidant.

This sparse and controverted evidence presented by Exelixis cannot carry its burden to prove that GRASTAR is a glidant in MSN's tablets.

E. MSN Will Not Induce Infringement.

Exelixis' sole theory of inducement is that MSN's supply of its tablets to Zydus, pursuant to the parties' license and supply agreement, will "induce the direct infringement of claim 3 of the '349 patent, including by Zydus, healthcare professionals, and/or patients in the United States." Br. at 15. In other words, Exelixis' inducement theory collapses into its direct infringement theory. But as explained above, Exelixis has failed to meet its burden of proving that MSN's tablets directly infringe. *Meyer Intell. Props. Ltd. v. Bodum, Inc.*, 690 F.3d 1354, 1366 (Fed. Cir. 2012) ("a finding of direct infringement is a prerequisite to a finding of inducement"). Further, as Exelixis admits, MSN identified GRASTAR to be a diluent in its tablets, and not a glidant. DFF ¶ 234; *see also Vita-Mix Corp. v. Basic Holding, Inc*., 581 F.3d 1317, 1328 (Fed. Cir. 2009) (finding no inducement where the alleged infringer "knew of its products' *potentially* infringing use").

V. CONCLUSION

MSN respectfully requests the Court find Exelixis has failed to meet its burden of proving that making, using, offering to sell, or selling in the United States, or importing into the United States MSN's tablets or the submission of MSN's ANDA will infringe, and that upon FDA approval MSN will induce infringement of, claim 3 of the '349 Patent.[12]

[12] MSN's Answer also seeks any appropriate relief under 35 U.S.C. § 285. *See* D.I. 9 in C.A. No. 22-cv-945, Prayers for Relief at f (August 9, 2022). No party has yet made a motion for fees, and, at this point, that issue is premature. MSN may seek fees as permitted by the Federal Rules.

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